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TITLE: Advanced MR Flow Imaging to Better Identify and Characterize High-Risk Dural Arteriovenous Fistulas

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CONTRACTING ORGANIZATION: University of California, San Francisco, California

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# REPORT DOCUMENTATION PAGE

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<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b> To overcome the challenges with MRI-based technique to diagnose dural arteriovenous fistulas DAVFs, which is the most dangerous vascular malformation affecting the brain and causes intracranial hemorrhage and mortality, our proposal is aimed to stratify risk of DAVF based on cortical venous drainage using advanced techniques including 7T MRI with ferumoxytol contrast agent and 3T MRI using gadolinium contrast agent. The proposed hypothesis is 7T MRI will be able to accurately identify DAVFs at high risk for causing hemorrhage compared to the "gold standard" diagnostic cerebral angiogram, and that 3T MRI using gadolinium contrast will provide comparable to 7T MRI primarily by leveraging acquisition of secondary hemodynamic characteristics of DAVFs. The study proposes to validate this hypothesis in 40 adult subjects. In this quarterly report, we present our progress with respect to the approved Statement of Work.						
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## 1. INTRODUCTION:

In the approved SOW, we proposed that (1) the improved spatial resolution of 7T MRI combined with the alternative contrast agent ferumoxytol will enable accurate direct visualization of cortical venous drainage (CVD) demonstrated on diagnostic cerebral angiography in patients with dural arteriovenous fistulas (DAVFs), and (2) 3T MRI using gadolinium contrast will provide a similar degree of diagnostic accuracy (relative to 7T MRI) to predict CVD by leveraging acquisition of secondary hemodynamic characteristics. The project's specific aims are (1) to develop advanced 7T MRI techniques to identify DAVF at a high risk for hemorrhage as confirmed by digital subtraction angiography (DSA), and (2) to develop 3T MRI to reliably predict CVD confirmed with DSA.

## 2. KEYWORDS:

Dural Fistula  
Cortical vein  
Dural venous sinus  
MRI  
4D Flow  
ICOSA6  
3D printing  
Hemodynamics  
Turbulent kinetic energy

## 3. ACCOMPLISHMENTS:

We report no significant changes in the project or its direction.

### What were the major goals of the project?

<b>Specific Aim 1:</b> Develop advanced 7T MRI techniques to improve dural arteriovenous fistula (DAVF) diagnosis and identify DAVF at a high risk for hemorrhage as confirmed by the gold standard digital subtraction angiography (DSA)	<b>Timeline</b>	<b>In progress</b>	<b>Completed</b>
<b>Major Task 1</b> Develop 3D printed in vitro models of DAVF that will be used to optimize MRI techniques in Aims 1 and 2	Months		
Subtask 1: Develop and test in vitro flow models	1 - 3		X
Subtask 2: Develop additional models as needed throughout the time period to investigate unanticipated in vivo findings.	As needed: 4 - 48	X	
Milestone #1: Submit manuscript describing in vitro flow models of DAVF	4 - 48	X	
<b>Major Task 2</b> Optimize 7T and 3T acquisitions using in vitro models			

<p>Subtask 1: Optimize imaging acquisition techniques using first in vitro models. Imaging techniques include phase contrast, pseudocontinuous arterial spin labelling, time of flight MRA, and 4D flow (3D velocity encoding across time).</p> <p>Compare hemodynamic variables obtained from MRI acquisitions with direct measurements and setting in the models. Perform repeated test measurements for a total of 27 acquisitions. Variables measured: (i) degree of outflow stenosis, (ii) flow velocity, (iii) venous pressure at the site of the fistula, (iv) venous pressures throughout the system, (v) volumetric flow rate of DAVF contributions, (vi) turbulent kinetic energy, (vii) cortical vein flow direction, and (viii) cortical vein pulsatility.</p>	1 - 6		X
<i>Milestone #2: Submit manuscript describing MRI imaging of in vitro DAVF models</i>	6	X	
<b>Major Task 3</b> Conduct initial feasibility studies to visualize large DAVF hemodynamics			
Subtask 1: Submit documents for local IRB review	1 - 3		X
Subtask 2: Submit IRB approval and necessary documents for HRPO review	3 - 6		X
<i>Milestone #3: HRPO approval received</i>			X
Subtask 3: Image first 3 subjects with large DAVF and review data for quality and consistency in group review sessions	6 - 9	X N = 2 of 3	
<p>Subtask 4: Address any issues discovered in Subtask 3 using computational fluid dynamics (CFD) and/or dye visualization experiments and optimize techniques</p> <p>Sites 1 (Dr. Amans's lab, including Mr. Valluru): Dye visualization experiments and data review</p> <p>Site 2 (Dr. Saloner's lab, including Dr. Kao): CFD experiments and data review</p>	6 - 10	X	X
Subtask 5 – compare data obtained at 7T and 3T with DSA data	6 - 12	X	
Site 1 (Dr. Amans's lab, including Dr. Jiang): obtain the DSA data, perform direct comparisons and statistical analysis.		X	
Site 2 (Dr. Saloner's lab): data review		X	
<i>Milestone #4: submit manuscript describing proof of concept techniques in vivo</i>	12	X	

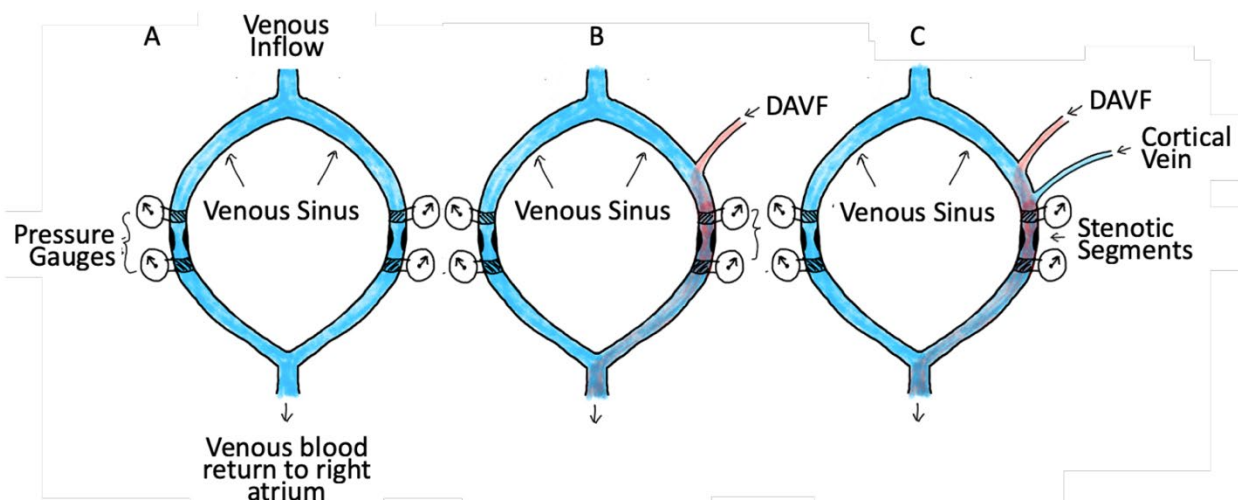
**What was accomplished under these goals?**

**Specific Aim 1 - Develop advanced 7T MRI techniques to identify DAVF at a high risk for hemorrhage.**

**Major Task 1: Develop 3D printed in vitro models of DAVF that will be used to optimize MRI techniques in Aims 1 and 2.**

**Subtask 1 (1 - 3 months):** Develop and test in vitro flow models.

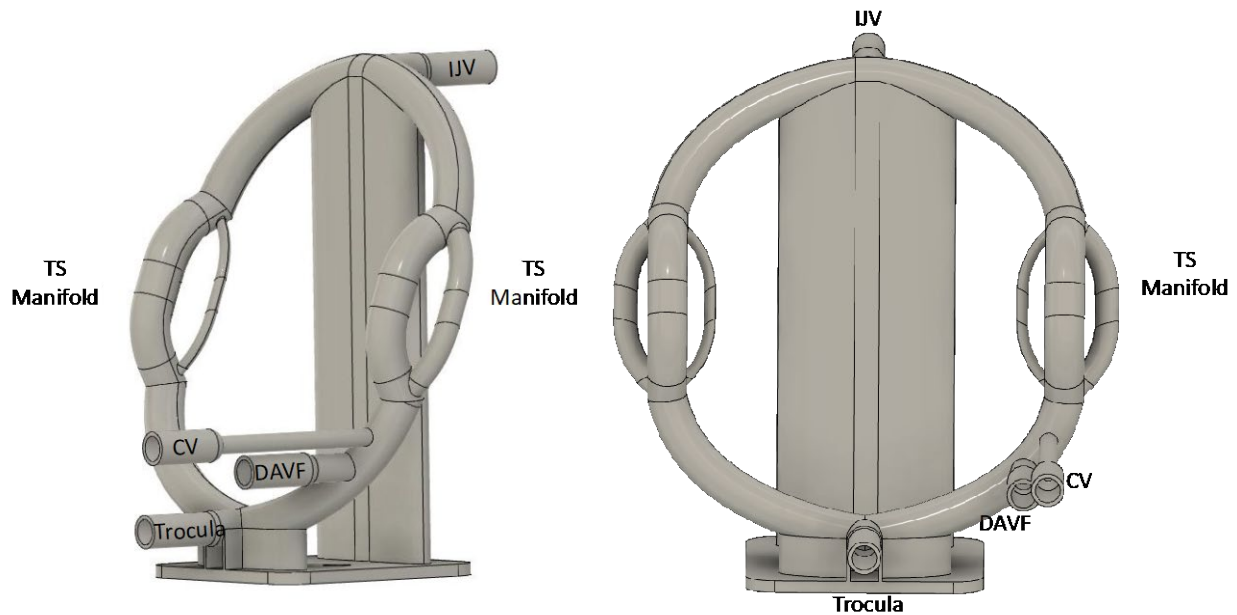
1) Specific objectives: To refine our 7T and 3T techniques for detection and to optimize our acceleration factors to shorten scan times, we proposed developing a series of 3D-printed flow models, each with an increasing level of complexity that simulate the complex hemodynamics within a DAVF (Fig 1). These in vitro models will serve as a reproducible test environment that allows for independent control of cerebral venous blood flow, degree of venous sinus stenosis causing resistance to typical antegrade venous outflow, arterial input function from the DAVF, as well as hydrostatic pressure in the cortical veins.



**Figure 1.** Schematics of 3D printed models of the dural venous sinuses with varying degrees of stenoses (labeled stenotic segments) (A), a simplified DAVF (B), and a DAVF with the potential for cortical venous drainage (C).

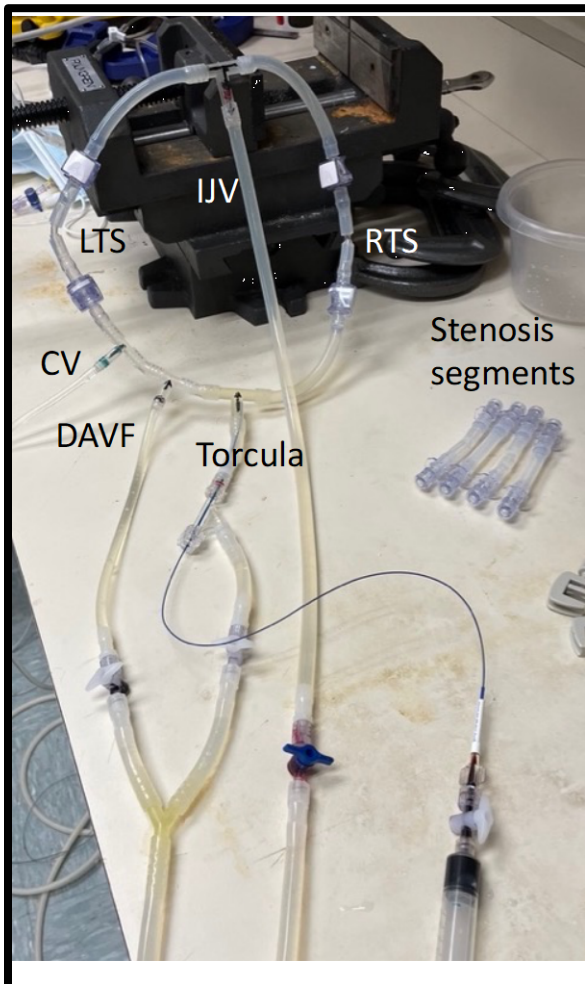
2) Major activities:

- We have designed an in vitro prototype that models the parallel flow circuit of the dural venous sinuses and allow for developing stenoses in each of the outflow limbs individually with preset degrees of stenosis. Both sides are designed to accommodate the stenosis segments to facilitate testing unilateral and bilateral stenosis conditions. With the help of flow regulating valves, this prototype (Fig 2) will allow us to test three distinct stenotic conditions in the lateral sinuses with stenosis segments measuring 8 mm diameter, 4 mm diameter, and 2.4 mm diameter (approximating no stenosis - 0%, moderate stenosis - 50%, and high-grade stenosis - 70%). The combination of 3 predetermined lumens in each limb yields 9 experimental geometries that will improve our ability to quantify disease in the dural venous sinuses.



**Figure 2.** Parallel flow circuit of the dural venous sinuses designed using AutoDesk Fusion 360. The model shows parallel limbs to mimic predetermined degrees of transverse sinus (TS) stenoses: 8 mm (0% - no stenosis), 4 mm (50% - moderate stenosis) and 2.4 mm (70% - severe stenosis). By employing flow regulating valves across the individual stenotic segments as well as the dural arterial venous fistula (DAVF) and cortical vein (CV), this design will facilitate performing multiple test conditions (normal, low risk DAVF with no CV drainage, and high risk DAVF with CV drainage). This model incorporates a 70-degree angle for TS mimicking in vivo condition with patient lying in supine position (representing the patient lying on the patient table for MRI or neurointervention in angiosuite).

- We initially proposed 3D printing this prototype with Agilus 30A, a flexible rubber-like material which we previously used for our venous models in the lab. However, the closed-loop design of this model posed a challenge to remove supports printed with Agilus 30 and thereby 3D print it successfully. We addressed this problem by designing and building an alternative prototype with off-the-shelf tubing materials and components. We connected this prototype into a flow circuit and performed flow visualization experiments to test its feasibility (Fig. 3).
- This tubing prototype allowed us to test our design that closely simulates the pathophysiology of DAVF under varying degrees of transverse sinus stenosis (Fig. 4). We will continue performing additional dye visualization experiments with this prototype to determine the optimal flow conditions for DAVF and cortical vein. We will then proceed to the next subtask of scanning the prototype with 3T and 7T MRI using 4D Flow sequences to evaluate hemodynamics of the model.



## Dye visualization setup

Flow rate = 7cc/s steady state

40% Glycerol in 60% water;  
Ferumoxylol bolus injection

Superior sagittal sinus (SSS) and  
bilateral venous sinus limb I.D. = 6.35  
mm

Dural Arteriovenous Fistula (DAVF) I.D.  
= 4.76 mm

Cortical vein (CV) I.D. = 3 mm

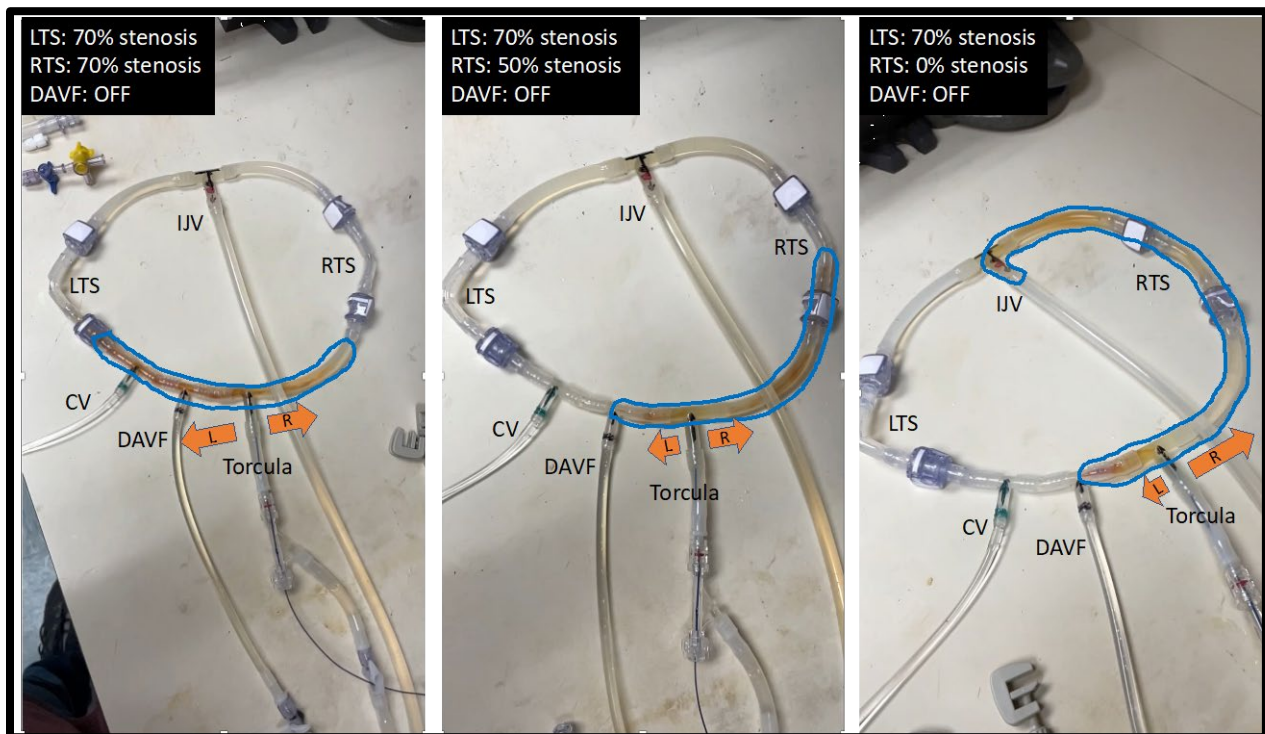
Stenosis segments:

Stenosis A: I.D. = 6.35 mm (0% stenosis)

Stenosis B: I.D. = 3 mm (53% stenosis)

Stenosis C: I.D. = 1.9 mm (70% stenosis)

**Figure 3.** DAVF tubing prototype built in lieu of 3D printed model. The transparent tubing allows excellent visualization of hemodynamics within the model. The model facilitates exchanging left and right transverse sinus (LTS and RTS respectively) sections with varying degrees of stenosis segments (0%, 50% and 70% stenosis). Conditions and parameters for dye visualization experiment setup are shown here. The blood analog solution (mixture of 40% glycerol and 60% water by volume) flows from SSS into Torcula at the characteristic venous flow rate of 7 cc/s where it splits to pass through left and right venous sinus limbs. CV and DAVF sections are designed to drain into the left limb. CV is connected to pressurized saline bag to determine the optimal pressure and flow rate required to mimic in vivo conditions. The blood analog solution will drain out of the model through the internal jugular vein (IJV), back to the reservoir connected to a programmable rotary pump (not shown in the figure).

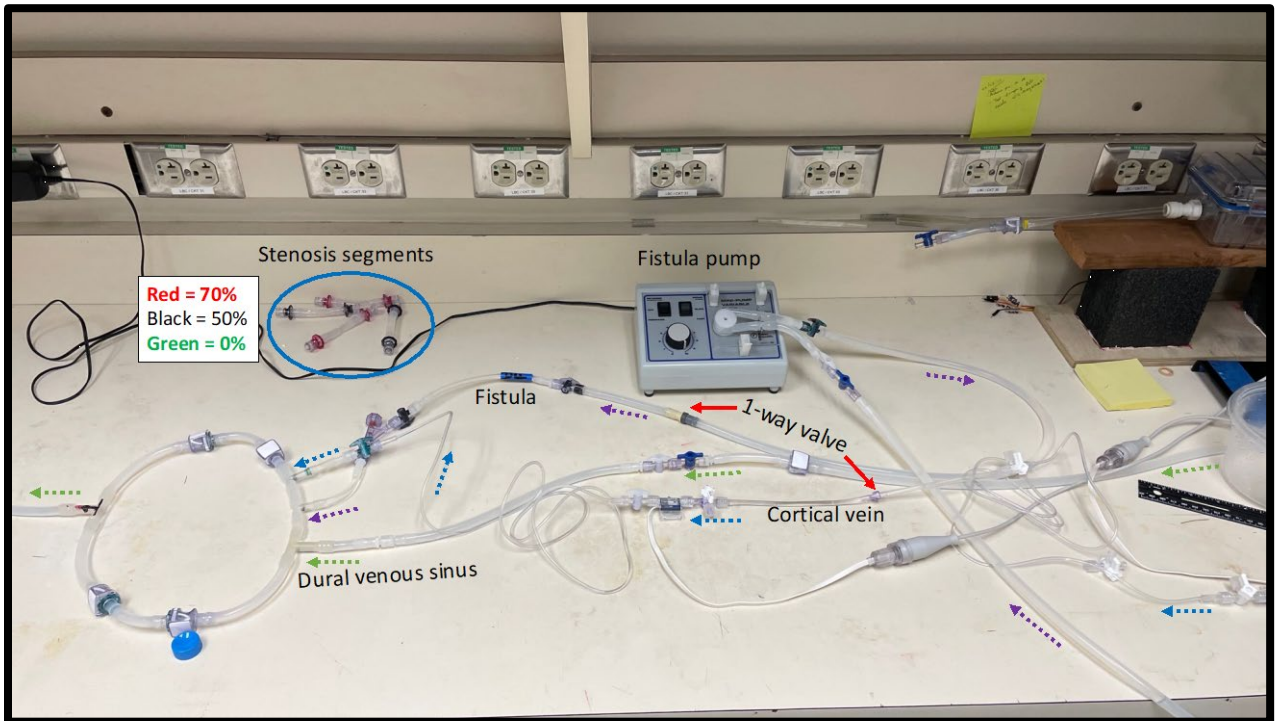


**Figure 4.** Dye visualization experiment. We are currently performing flow optimization experiments with our tubing prototype. The figure illustrates flow through the model when the degree of right transverse sinus (RTS) stenosis is varied between 70% (left frame), 50% (middle frame) and 0% (right frame) stenosis while the left transverse sinus (LTS) stenosis was kept constant at 70%. A bolus of Ferumoxytol was injected into the torcula using a catheter while the flow through DAVF was turned OFF. The flow of Ferumoxytol could be easily visualized (highlighted in blue) in the transparent model. When both sides were stenosed equally (left frame), the flow rate on either side seemed to be similar as indicated by the length of orange arrows. When the RTS stenosis was reduced to 50% (middle frame), the flow rate was marginally higher on the less stenotic right side. And when the RTS stenosis was eliminated (right frame), the flow rate of the dye was significantly faster on the right side as indicated by the length of the orange arrow, as well as the extent of the blue highlighted region encompassing Ferumoxytol. The CV was connected to a saline bag and was pressurized to 300 mmHg. This pressure turned out to be quite high as we didn't notice any back flow into the CV even under bilateral high-risk stenosis (70% LTS and 70% RTS) with DAVF turned ON (not shown in the picture).

- 3) Key outcomes: Development and testing of in vitro flow models is completed.
- 4) Goals not met: Nothing to report.

**Subtask 2 (4 - 48 months):** Develop additional models as needed throughout the time period to investigate unanticipated in vivo findings.

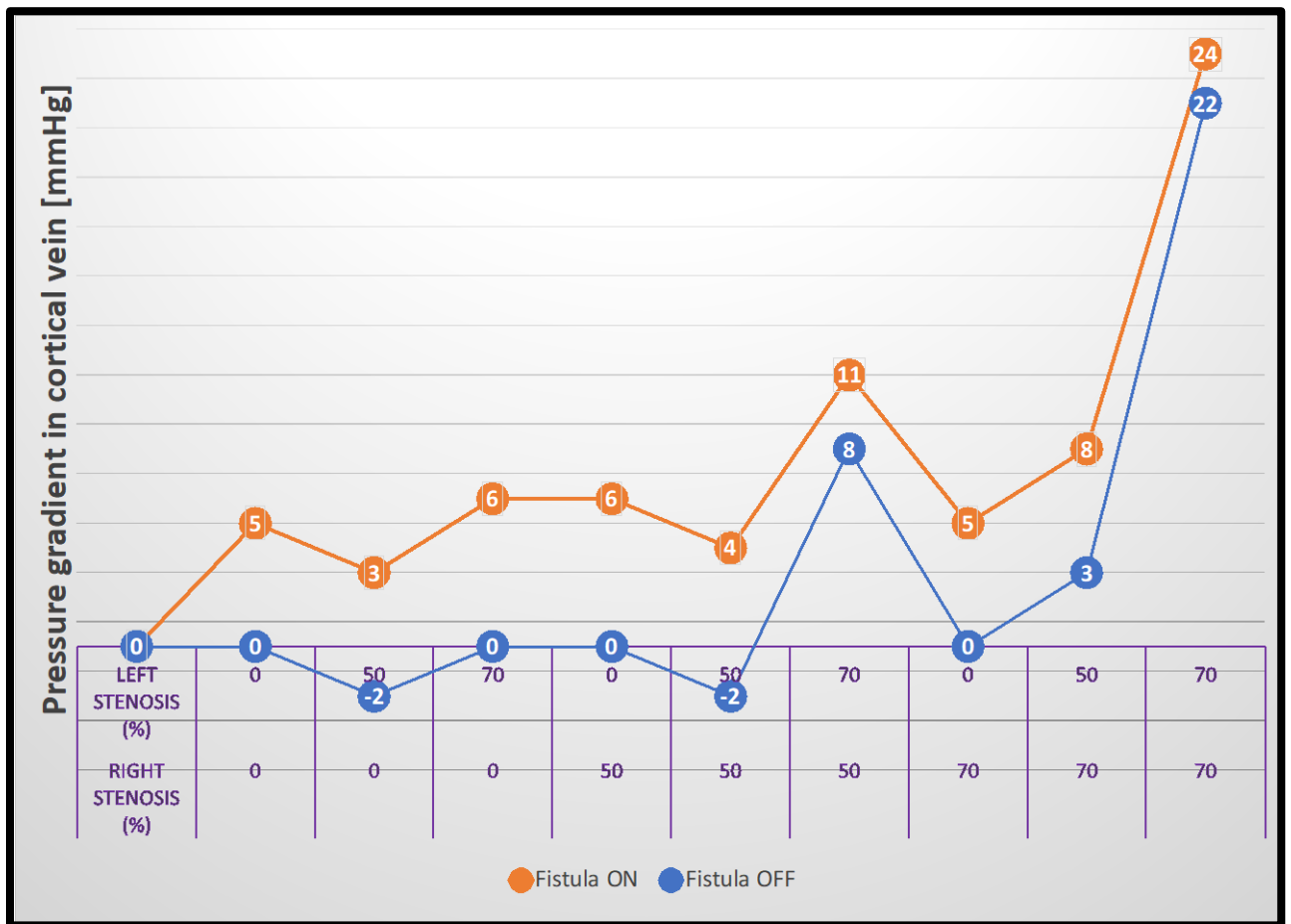
- 1) Specific objectives: This activity is proposed to be performed as needed in months 4 - 48.
- 2) Major activities: Based on the feedback from the experiments performed in the Major Task 1 - Subtask 1, we incorporated additional elements into our prototype design (Figs. 5 and 6). We tested this modified prototype by conducting a carefully designed manometry experiment to study the impact of varying degrees of transverse sinus stenoses on the flow within the cortical vein under the absence/presence of DAVF. The results of this study are presented in Fig. 7.



**Figure 5.** The tubing prototype shown in Fig. 3 was modified to more accurately represent the DAVF circuit. Two separate one-way valves are added to the fistula and cortical vein segments respectively to prevent the backflow of the blood analog fluid in the control (no stenosis) state. A separate peristaltic pump is employed to circulate flow through the DAVF/Fistula segment. The cortical vein segment is connected to a pressurized bag filled with the blood analog fluid (Fig.6).



**Figure 6.** The bag filled with blood analog solution is pressurized to deliver the flow through the cortical vein model at a velocity of 1 cm/s. As the degree of stenosis is varied within each venous limb, the pressure before and after the one-way valve within the cortical vein is measured and displayed on the monitor in real-time.



**Figure 7.** Impact of DAVF (Fistula ON vs. Fistula OFF) on the cortical vein (CV) with varying degrees of transverse sinus (TS) stenosis on either side of the cerebral venous outflow tract. Left side = TS same side as CV, Right side = TS opposite side of CV. Stenosis grade: 0% = None, 50% = Moderate, 70% = High. The presence of fistula resulted in an increase of the pressure gradient by 5 mmHg when there is no TS stenosis (L = 0, R = 0). When a moderate TS stenosis was introduced, the presence of fistula led to a pressure gradient within the CV by 5 – 6 mmHg (L = 0, R = 50; L = 50, R = 50; L = 50, R = 0), similar to the no stenosis condition. When the TS stenosis was high-grade but present only on either side, the fistula contributed to the similar increase in the pressure gradient by 5 – 6 mmHg (L = 0, R = 70; L = 70, R = 0), as seen in the previous states. When the TS stenosis was moderate on the same side as CV and high-grade on the opposite side (L = 50, R = 70), a pressure gradient of 3 mmHg was observed within the CV without fistula, and 8 mmHg with fistula, resulting in an increase in pressure gradient by 5 mmHg. When the TS stenosis was high-grade on the same side and moderate or high-grade on the opposite side (L = 70, R = 50; L = 70, R = 70), the impact of fistula seems to be dwarfed by the extent of stenosis resulting in much higher absolute pressure gradients and significantly smaller relative pressure gradients (11 - 8 = 3 mmHg and 24 - 22 = 2 mmHg) between the fistula ON and OFF states respectively.

- 3) **Key outcomes:** The modified prototype proved to be a better approximation of the in vivo DAVF condition. This version of the prototype facilitated the use of patient characteristic flow rates within the venous outflow tract and the cortical vein. The mini peristaltic pump used to circulate flow within the DAVF segment was only capable of delivering a fixed flow rate of 1.5 cc/s. In the next iteration, we will upgrade this to a pump that's capable of providing a variable flow rate to quantitatively determine the effect of the DAVF in addition to its presence on the cortical vein.
- 4) **Goals not met:** Nothing to report.

**Milestone #1:** Submit manuscript describing in vitro flow models of DAVF.

The manometry data from our in vitro models is encouraging. We will next perform dye visualization studies to validate our manometry observations. This will provide us ample data to submit a manuscript as proposed. For this time period, this is reported as a goal in progress.

## Major Task 2: Optimize 7T and 3T acquisitions using in vitro models.

**Subtask 1 (1 - 6 months):** Optimize imaging acquisition techniques using first in vitro models. Imaging techniques include phase contrast, pseudo-continuous arterial spin labelling, time of flight MRA, and 4D flow (3D velocity encoding across time).

- 1) Specific objectives: Compare hemodynamic variables obtained from MRI acquisitions with direct measurements and setting in the models. Perform repeated test measurements for a total of 27 acquisitions. Variables measured: (i) degree of outflow stenosis, (ii) flow velocity, (iii) venous pressure at the site of the fistula, (iv) venous pressures throughout the system, (v) volumetric flow rate of DAVF contributions, (vi) turbulent kinetic energy, (vii) cortical vein flow direction, and (viii) cortical vein pulsatility.
- 2) Major activities: We are simultaneously executing Major Task 1 - Subtask 2 and Major Task 2 – Subtask 1. We have our modified version of the prototype ready for scanning. We are getting ready to acquire 7T and 3T MRI data using this model to tune VENC, spatial resolution, and acceleration factors for determining the blood flow in the native dural venous sinuses. We will also perform testing using arterial input that is 50% above and below the derived in vivo values from step 3 once we upgrade our DAVF pump. We will then proceed to obtain pressure maps in this model at 7T and 3T to compare with catheter-based manometry experiments.
- 3) Key outcomes: Nothing to report.
- 4) Goals not met: Nothing to report.

**Milestone #2:** Submit manuscript describing MRI imaging of in vitro DAVF models

Once all the goals in Major Tasks 1 and 2 are met, we will prepare and submit the manuscript as proposed. For this time period, this is reported as a goal in progress.

## Major Task 3: Conduct initial feasibility studies to visualize large DAVF hemodynamics

**Subtask 1 (1 - 3 months):** Submit documents for local IRB review

- 1) Specific objectives: Submit documents to local IRB review.
- 2) Major activities: We worked with our institutional IRB to pursue this activity.
- 3) Key outcomes: We received the approval from local IRB.
- 4) Goals not met: Nothing to report.

**Subtask 2 (3 - 6 months):** Submit IRB approval and necessary documents for HRPO review.

- 1) Specific objectives: Submit IRB approval and necessary documents for HRPO review.
- 2) Major activities: We worked with our local IRB and HRPO to submit the IRB approval and all the required documents for HRPO review.
- 3) Key outcomes: We received the approval from HRPO.
- 4) Goals not met: Nothing to report.

**Milestone #3:** HRPO approval received

We achieved this milestone. For this time period, this is reported as completed.

**Subtask 3 (6 – 9 months):** Image first 3 subjects with large DAVF and review data for quality and consistency in group review sessions.

- 1) Specific objectives: Image first 3 subjects with large DAVF and review data for quality and consistency in group review sessions.

- 2) Major activities: We started recruiting subjects and imaged first two subjects with a large DAVF. Once we image one more subject, we will schedule group review sessions to review the data for quality and consistency.
- 3) Key outcomes: Nothing to report.
- 4) Goals not met: We are yet to recruit the third subject.

**STATUS:**

			Enter information regarding number of subjects				
HRPO Protocol Number	Protocol PI Name	Organization (Site)	# Target	# Enrolled	# Completed	# Screened	# Recruited
HRPO Log Number E02403.1a	Matthew Amans, MD	University of California, San Francisco	3 of 40	2 of 3	2 of 3	2 of 3	2 of 3

**Demographics**

DAVF Enrollment Report										
Racial categories	Not Hispanic or Latino			Hispanic or Latino			Unknown / Not Reported Ethnicity			Total
	Female	Male	Unkn own / Not Repo rted	Female	Male	Unkn own / Not Repo rted	Female	Male	Unkn own / Not Repo rted	
American Indian /Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	1	0	0	0	0	0	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	1	0	0	0	0	0	0	0	0	1
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
<b>Total</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2</b>

**Subtask 4 (6 – 10 months):** Address any issues discovered in Subtask 3 using computational fluid dynamics (CFD) and/or dye-dilutional experiments and optimize techniques.

- 1) Specific objectives: Address any issues discovered in Subtask 3 that need improvement.
- 2) Major activities: Once we complete Subtask 3, we will evaluate the in vivo 4D Flow data from the first three subjects and compare it with CFD data to identify differences between them and take necessary actions to optimize the 4D Flow data acquisition protocol.
- 3) Key outcomes: Nothing to report.
- 4) Goals not met: This subtask is contingent upon the recruitment of the third subject.

**Subtask 5 (6 – 12 months):** Compare data obtained at 7T and 3T with DSA data

- 1) Specific objectives: Perform direct comparisons of 3T, 7T and DSA data.
- 2) Major activities: We will compare and evaluate the 3T, 7T and DSA data obtained from the first three subjects to identify key differences between them.
- 3) Key outcomes: Nothing to report.
- 4) Goals not met: This subtask is contingent upon the recruitment of the third subject.

## Summary

We are on track with the stated goals and subtasks as listed in this report. While we experienced some technical challenges in Major Task 1 in third quarter (Q3), we addressed them using alternate approaches as mentioned and were able to complete the preliminary design and testing of the prototype in the fourth quarter (Q4). We learnt a great deal from the experiments with our initial prototype in Major Task 1 - Subtask 1, and incorporated design changes into our next iteration as reported in Major Task 1 – Subtask 2. We will image this modified prototype as described in Major Task 2 – Subtask 1. We have completed Major Task 3 – Subtask 1 and Major Task 3 – Subtask 2. For Major Task 3 – Subtask 3, we recruited 2 of 3 subjects and are slightly delayed with our subject enrollment as per the approved SOW.

## Conclusion

This is our fourth quarterly report (first Annual report), and it reflects our progress with respect to the approved SOW.

## What opportunities for training and professional development has the project provided?

Nothing to Report

## How were the results disseminated to communities of interest?

Nothing to Report

## What do you plan to do during the next reporting period to accomplish the goals?

We will complete the Major Task 2 that is in progress including submission milestones 1 and 2. We are on track with respect to the Major Task 3 and will complete Subtasks 3 - 5 by the end of the next reporting period (Q5).

## 4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

## What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

## What was the impact on other disciplines?

Nothing to Report

**What was the impact on technology transfer?**

Nothing to Report

**What was the impact on society beyond science and technology?**

Nothing to Report

## **5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change.**

Nothing to Report

**Actual or anticipated problems or delays and actions or plans to resolve them.**

Nothing to Report

**Changes that had a significant impact on expenditures**

Nothing to Report

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report

**Significant changes in use or care of human subjects**

Nothing to Report

**Significant changes in use or care of vertebrate animals**

Nothing to Report

**Significant changes in use of biohazards and/or select agents**

Nothing to Report

**6. PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

**Publications, conference papers, and presentations:**

Nothing to Report

**Journal publications.**

Nothing to Report

**Books or other non-periodical, one-time publications.**

Nothing to Report

**Other publications, conference papers and presentations.**

Nothing to Report

**Website(s) or other Internet site(s).**

Nothing to Report

**Technologies or technique.**

Nothing to Report

## Inventions, patent applications, and/or licenses.

Nothing to Report

## Other Products.

As a part of the Major Task 1, this project resulted in 3D printed vitro flow models during this quarter.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

For the dates: 07/01/2022 – 09/30/2022, please see the efforts of individuals in the table below.

Name	Project Role	Researcher Identifier	% Effort	Contribution to Project
Keerthi Valluru, MS	Research and Development Engineer	0000-0002-8627-973X	100	Mr. Valluru has performed model design, prototyping, experiments and manometry data analysis.
Megan Ballweber, BS	Clinical Research Coordinator		13.13	Ms. Ballweber is instrumental in recruiting and imaging patients for this study.
Evan Kao, PhD	Postdoctoral scholar		40	Dr. Kao has developed the software tool to determine noninvasive pressure readings from MRI data.
Adelyn Tu-Chan, DO	Physician		10	Dr. Tu-Chan oversaw the subject recruitment.
Fei Jiang, PhD	Co-I		3.5	Dr. Jiang has assisted the PI in the several complex statistical analyses that will be used to best identify if MRI can accurately detect high risk features in DAVF.
David Saloner, PhD	PI – Site 2		22.98	Dr. Saloner supervised the software tool development for

				pressure estimations and MR imaging of the first two subjects.
Matthew Amans, MD	PI – Site 1		20.01	Dr. Amans oversaw the model designs, dye visualization and manometry experiments, and subject recruitment.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

**What other organizations were involved as partners?**

Nothing to Report

**8. SPECIAL REPORTING REQUIREMENTS**

Nothing to Report

**9. APPENDICES:**

Nothing to Report